

## ANNEXES

filed with the letter  
of 03.10.01

## AMENDMENT

To: Examiner of the Patent Office

1. Identification of the International Application  
PCT/JP00/04991

## 2. Applicant

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3. Item to be Amended  
Claims

## 4. Subject Matter of Amendment

The expression " (When either  $R_2$  or  $R_3$  does not form, together with  $Z$ ,  $R_1$  and  $X$ , a saturated or unsaturated five- to eight-membered cyclic group,  $Ar$  is not a substituted thiazolyl group.)" should be added in the Claim 1 on page 484 (6th to 9th line).

The expression " (When either  $R_{2a}$  or  $R_{3a}$  does not form, together with  $Z_a$ ,  $R_{1a}$  and  $X_a$ , a saturated or unsaturated five- to eight-membered cyclic group,  $Ar$  is not a substituted thiazolyl group.)" should be added in the Claim 2 on page 491 (23rd to 24th line) and on page 491/1 (1st to 2nd line).

The expression " (Herein, a nitrogen-containing heteroaromatic ring group does not include a quinolyl group.)" should be added in the Claim 4 on page 497 (23rd to 25th line), and the expression " (When  $R_{2p}$  does not form, together with the binding carbon atom,  $R_{1p}$  and  $X_p$ , a saturated or unsaturated five- to six-membered cyclic group,  $Ar$  is not a substituted thiazolyl group.)" should be added in the Claim 4 on page 498 (6th to 9th line).

The expression " (When either  $R_2$  or  $R_3$  does not form, together with Z,  $R_1$  and X, a saturated or unsaturated five- to eight-membered cyclic group, Ar is not a substituted thiazolyl group.)" should be added in the Claim 7 on page 526 (6th to 9th line).

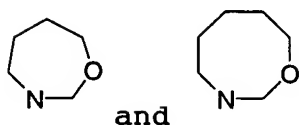
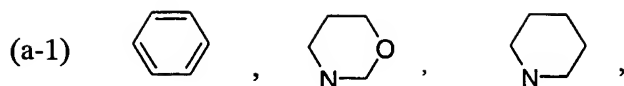
The expression " (When either  $R_2$  or  $R_3$  does not form, together with Z,  $R_1$  and X, a saturated or unsaturated five- to eight-membered cyclic group, Ar is not a substituted thiazolyl group.)" should be added in the Claim 10 on page 541 (23rd to 25th line).

#### 5. List of Attached Documents

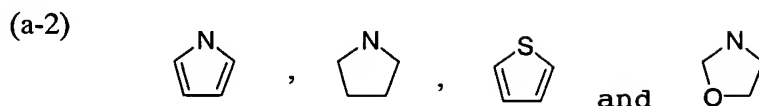
Replacement sheet of page 484 and 484/1 (Claim1); 491 and 491/1 (Claim2); 497, 497/1, 498 and 498/1 (Claim4); 526 and 526/1 (Claim7); and 541 and 541/1 (Claim10)

alkanoylamidino lower alkyl group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a hydroxyimino group and a lower alkoxyimino group, and a substituent selected from groups  
 5 represented by the formula  $Y_1-W_1-Y_2-R_p$  (wherein:  $R_p$ ,  $W_1$ ,  $Y_1$  and  $Y_2$  have the same meanings as stated above) (When either  $R_2$  or  $R_3$  does not form, together with  $Z$ ,  $R_1$  and  $X$ , a saturated or unsaturated five- to eight-membered cyclic group,  $Ar$  is not a substituted thiazolyl group.);  $R_4$  and  $R_5$   
 10 are each, the same or different, a hydrogen atom, halogen atoms, a hydroxy group, an amino group, or a substituent represented by the formula  $Y_3-W_2-Y_4-R_s$  (wherein:  $R_s$ ,  $W_2$ ,  $Y_3$  and  $Y_4$  have the same meanings as stated above), or any of a lower alkyl group, an aryl group or an aralkyl group which  
 15 may be substituted with one to three of the same or different substituent(s) selected from both a set of groups consisting of a lower alkyl group, a cyano group, a nitro group, a carboxyl group, a carbamoyl group, a formyl group, a lower alkanoyl group, a lower alkanoyloxy group, a  
 20 hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy group, a lower alkoxy carbonyl group, lower alkoxy carbonylamino group, a lower alkoxy carbonylamino lower alkyl group, a lower  
 25 alkyl carbamoyl group, a di-lower alkyl carbamoyl group, a carbamoyloxy group, a lower alkyl carbamoyloxy group, di-lower alkyl carbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower

alkylamino lower alkyl group, a di-lower alkylamino lower alkyl group, a tri-lower alkylammonio lower alkyl group, a lower alkanoylamino group, an aroylamino group, a lower



and



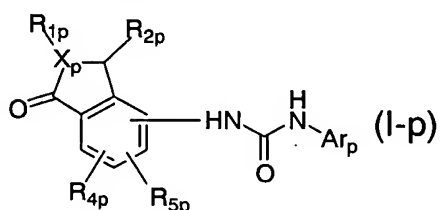
which may have one or more kinds of hetero atom(s), and  
 5 which may be substituted with one to three of the same or  
 different substituent(s) selected both from a set of groups  
 consisting of a lower alkyl group, a spiro cyclo lower  
 alkyl group which may be substituted, a hydroxy group, a  
 hydroxy lower alkyl group, lower alkoxy group, a lower  
 10 alkoxy carbonyl group, a lower alkoxy carbonylamino group, a  
 lower alkoxy carbonylamino lower alkyl group, a lower  
 alkyl carbamoyl group, a lower alkyl carbamoyloxy group, a  
 lower alkylamino group, a di-lower alkylamino group, an  
 amino lower alkyl group, a lower alkylamino lower alkyl  
 15 group, a di-lower alkylamino lower alkyl group, a lower  
 alkanoylamino group and an aroylamino group, and groups  
 represented by the formula  $Y_{1a}-W_{1a}-Y_{2a}-R_{pa}$  (wherein:  $R_{pa}$ ,  $W_{1a}$ ,  
 $Y_{1a}$  and  $Y_{2a}$  have the same meanings as stated above), and,  
 furthermore, which may be fused with a cyclo lower alkyl  
 20 group, an aryl group, a heteroaromatic ring group selected  
 from a group of a pyridyl group and a pyrazolyl group, and  
 an aliphatic heterocyclic group selected from a group of  
 piperidinyl group and a pyrrolidinyl group (When either  $R_{2a}$   
 or  $R_{3a}$  does not form, together with  $Z_a$ ,  $R_{1a}$  and  $X_a$ , a

saturated or unsaturated five- to eight-membered cyclic group, Ar is not a substituted thiazolyl group.);  $R_{4a}$  and  $R_{5a}$  are each, the same or different, a hydrogen atom or a

or a lower alkyl group, an aryl group or an aralkyl group which may be substituted with one to three of the same or different substituent(s) selected from a set of groups consisting of substituents comprising any of a hydrogen  
 5 atom, halogen atoms or a substituent represented by the formula  $Y_{3b}-W_{2b}-Y_{4b}-R_{sb}$  (wherein:  $R_{sb}$ ,  $W_{2b}$ ,  $Y_{3b}$  and  $Y_{4b}$  have the same meanings as stated above), or a substituent selected from a set of groups consisting of a lower alkyl group, a hydroxy lower alkyl group, a halo lower alkyl group, a  
 10 lower alkoxycarbonylamino group, a lower alkoxycarbonylamino lower alkyl group, a lower alkylcarbamoyl group, a lower alkylamino group, a lower alkylamino lower alkyl group, a lower alkanoylamino group, and an aroylamino group,; and the formula  $---$  means a  
 15 single bond or a double bond.

4. A compound according to any one of claim 1 to claim 3, having a structure of Formula (I-p) and pharmaceutically acceptable salts thereof,

20 Formula (I-p)



wherein:  $Ar_p$  is a nitrogen-containing heteroaromatic ring group which may be substituted (Herein, a nitrogen-containing heteroaromatic ring group does not include a  
 25 quinolyl group.),  $X_p$  is a carbon atom (CH) or a nitrogen atom,  $R_{1p}$  is a hydrogen atom or a lower alkyl group which

may be substituted,  $R_{2p}$  is a hydrogen or an oxo group (which forms carbonyl group, together with the carbon



atom on which it stands), or forms, together with the carbon atom on which it stands,  $R_{1p}$  and  $X_p$ , a saturated or an unsaturated five- or six-membered cyclic group which may have one or more kinds of hetero atom(s) selected from a group of a nitrogen atom and a sulfur atom or which may be substituted (When  $R_{2p}$  does not form, together with the binding carbon atom,  $R_{1p}$  and  $X_p$ , a saturated or unsaturated five- to six-membered cyclic group, Ar is not a substituted thiazolyl group.);  $R_{4p}$  and  $R_{5p}$  are each, the same or different, any of a hydrogen atom, halogen atoms, a hydroxy group, an amino group or a lower alkyl group, an aryl group or an aralkyl group which may be substituted.

5. A compound according to claim 1, wherein the compound is

15 N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(2-octylaminomethyl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(2-methyl-4,4-dimethylpentylaminomethyl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(5-methoxyindan-2-ylaminomethyl)pyrazol-3-yl)urea,

20 N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(2-methylindan-2-ylaminomethyl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(5-chloroindan-2-ylaminomethyl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(6-methylpyridin-2-yl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(pyrrolidin-2-yl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(t-butylaminomethyl)pyrazol-3-yl)urea, N'-(pyrrolidino[2,1-

b]isoindolin-4-on-8-yl)-N-(5-(pyrazolo[5,4-b]pyridin-3-yl)urea, N'-(pyrrolidino[2,1-b]isoindolin-4-on-8-yl)-N-(5-(1-hydroxymethylcyclopentylaminomethyl)pyrazol-3-yl)urea,

group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a hydroxyimino group and a lower alkoxyimino group, and a substituent or substituents selected from groups represented by the formula  $Y_1-W_1-Y_2-R_p$  (wherein:  $R_p$ ,  $W_1$ ,  $Y_1$  and  $Y_2$  have the same meanings as stated above) (When either  $R_2$  or  $R_3$  does not form, together with  $Z$ ,  $R_1$  and  $X$ , a saturated or unsaturated five- to eight-membered cyclic group,  $Ar$  is not a substituted thiazolyl group.);  $R_4$  and  $R_5$  are each, the same or different, a hydrogen atom, halogen atoms, a hydroxy group, an amino group, or a substituent represented by the formula  $Y_3-W_2-Y_4-R_s$  (wherein:  $R_s$ ,  $W_2$ ,  $Y_3$  and  $Y_4$  have the same meanings as stated above), or any of a lower alkyl group, an aryl group or an aralkyl group which may be substituted with one to three of the same or different substituent(s) selected from both a set of groups consisting of a lower alkyl group, a cyano group, a nitro group, a carboxyl group, a carbamoyl group, a formyl group, a lower alkanoyl group, a lower alkanoyloxy group, a hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy group, a lower alkoxy carbonyl group, lower alkoxy carbonylamino group, a lower alkoxy carbonylamino lower alkyl group, a lower alkyl carbamoyl group, a di-lower alkyl carbamoyl group, a carbamoyloxy group, a lower alkyl carbamoyloxy group, di-lower alkyl carbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower alkylamino lower alkyl group, a

di-lower alkylamino lower alkyl group, a tri-lower alkylammonio lower alkyl group, a lower alkanoylamino group, an aroylamino group, a lower alkanoylamidino lower alkyl

substituted, a hydroxyl group, a cyano group, halogen atoms, a nitro group, a carboxyl group, a carbamoyl group, a formyl group, a lower alkanoyl group, a lower alkanoyloxy group, a hydroxy lower alkyl group, a cyano lower alkyl group, a halo lower alkyl group, a carboxy lower alkyl group, a carbamoyl lower alkyl group, lower alkoxy group, a lower alkoxycarbonyl group, lower alkoxycarbonylamino group, a lower alkoxycarbonylamino lower alkyl group, a lower alkylcarbamoyl group, a di-lower alkylcarbamoyl group, a carbamoyloxy group, a lower alkylcarbamoyloxy group, di-lower alkylcarbamoyloxy group, an amino group, a lower alkylamino group, a di-lower alkylamino group, a tri-lower alkylammonio group, an amino lower alkyl group, a lower alkylamino lower alkyl group, a di-lower alkylamino lower alkyl group, a tri-lower alkylammonio lower alkyl group, a lower alkanoylamino group, an aroylamino group, a lower alkanoylamidino lower alkyl group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, a lower alkylsulfonylamino group, a hydroxyimino group and a lower alkoxyimino group, and a substituent selected from groups represented by the formula  $Y_1-W_1-Y_2-R_p$  (wherein:  $R_p$ ,  $W_1$ ,  $Y_1$  and  $Y_2$  have the same meanings as stated above) (When either  $R_2$  or  $R_3$  does not form, together with  $Z$ ,  $R_1$  and  $X$ , a saturated or unsaturated five- to eight-membered cyclic group,  $Ar$  is not a substituted thiazolyl group.);  $R_4$  and  $R_5$  are each, the same or different, a hydrogen atom, halogen atoms, a hydroxy group, an amino group, or a substituent represented by the formula  $Y_3-W_2-Y_4-R_s$  (wherein:  $R_s$ ,  $W_2$ ,  $Y_3$  and  $Y_4$  have the same meanings as stated above), or any of a

lower alkyl group, an aryl group or an aralkyl group which may be substituted with one to three of the same of different substituent or substituents selected from both a